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(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SANGANEE, Hitesh** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). **SPRINGTHORPE, Brian** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

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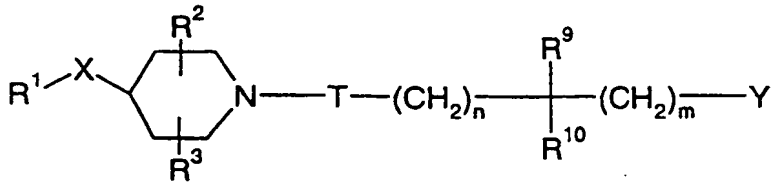
(54) Title: CHEMICAL COMPOUNDS



(I)

(57) Abstract: The invention concerns compounds of formula (I), and their use in therapy, particularly in the modulation of CCR3 activity.

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CHEMICAL COMPOUNDS

The present invention concerns piperidine derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in WO99/38514, WO99/04794 and WO00/29377.

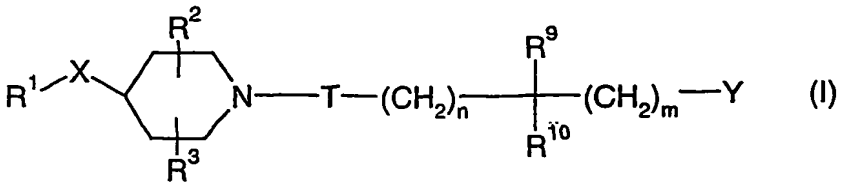
Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The present invention provides a compound of formula (I):



(I)

wherein:

m and n are, independently, 0, 1, 2, 3 or 4;

X is CH_2, CO, O, S, S(O), $S(O)_2$ or NR^6;

Y is $NR^4S(O)_2R^5$ or $S(O)_2NR^4R^5$;

T is C=O or CR^7R^8;

R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl;

R^2 and R^3 are, independently, hydrogen or C_{1-6} alkyl;

R^4 and R^6 are, independently, hydrogen or C_{1-6} alkyl (optionally substituted with aryl);

R^5 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^{11}, aryl or heterocyclyl}, C_{3-10} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, C_{3-7} cycloalkenyl {optionally substituted by C_{1-6} alkyl or aryl}, aryl or heterocyclyl; or, when Y is $S(O)_2NR^4R^5$, R^5 may also be hydrogen;

R^7, R^8, R^9 and R^{10} are, independently, hydrogen or C_{1-6} alkyl (optionally substituted with aryl);

wherein the foregoing aryl and heterocyclyl moieties are, independently, optionally substituted by one or more of halo, cyano, nitro, hydroxy, $S(O)_qR^{11}$, $OCONR^{12}R^{13}$, $NR^{14}R^{15}$, $NR^{16}COR^{17}$, $NR^{18}CONR^{19}R^{20}$, $SO_2NR^{21}R^{22}$, $NR^{23}SO_2R^{24}$, $CONR^{25}R^{26}$, COR^{27}, CO_2R^{28}, $OCOR^{29}$, $NR^{30}CO_2R^{31}$, C_{1-6} alkyl (itself optionally substituted with halo, C_{1-6} alkoxy, C_{3-10} cycloalkyl, $CO_2(C_{1-6}$ alkyl), $OCO(C_{1-6}$ alkyl), SO_2R^{32}, $CONR^{33}R^{34}$, phenyl, phenoxy, heterocyclyl or heterocyclyloxy), C_{3-10} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, methylenedioxy, phenyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, heterocyclyl, heterocyclyloxy or heterocyclyl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heterocyclyl moieties are optionally substituted with halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, SO_2NH_2, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $CONH_2$, $CONH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHCO(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), $CO(C_{1-4}$ alkyl), CF_3 or OCF_3;

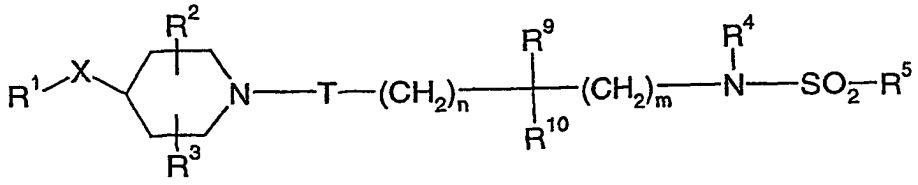
R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{33} and R^{34} are, independently, hydrogen, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

R^{11}, R^{24} and R^{32} are, independently, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

k and q are, independently, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof; or a solvate thereof.

In one particular aspect the present invention provides a compound of formula (I')



(I')

wherein:

m and n are, independently, 0, 1, 2, 3 or 4;

X is CH_2, CO, O, S, S(O), $S(O)_2$ or NR^6;

T is C=O or CR^7R^8;

R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl;

R^2 and R^3 are, independently, hydrogen or C_{1-6} alkyl;

R^4 and R^6 are, independently, hydrogen or C_{1-6} alkyl (optionally substituted with aryl);

R^5 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^{11}, aryl or heterocyclyl}, C_{3-10} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, C_{3-7} cycloalkenyl {optionally substituted by C_{1-6} alkyl or aryl}, aryl or heterocyclyl;

R^7, R^8, R^9 and R^{10} are, independently, hydrogen or C_{1-6} alkyl (optionally substituted with aryl);

wherein the foregoing aryl and heterocyclyl moieties are, independently, optionally substituted by one or more of halo, cyano, nitro, hydroxy, $S(O)_qR^{11}$, $OCONR^{12}R^{13}$, $NR^{14}R^{15}$, $NR^{16}COR^{17}$, $NR^{18}CONR^{19}R^{20}$, $SO_2NR^{21}R^{22}$, $NR^{23}SO_2R^{24}$, $CONR^{25}R^{26}$, COR^{27}, CO_2R^{28}, $OCOR^{29}$, $NR^{30}CO_2R^{31}$, C_{1-6} alkyl (itself optionally substituted with halo, C_{1-6} alkoxy, C_{3-10} cycloalkyl, $CO_2(C_{1-6}$ alkyl), $OCO(C_{1-6}$ alkyl), SO_2R^{32}, $CONR^{33}R^{34}$, phenyl, phenoxy, heterocyclyl or heterocyclyloxy), C_{3-10} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, methylenedioxy, phenyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, heterocyclyl, heterocyclyloxy or heterocyclyl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heterocyclyl moieties are optionally substituted with halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, SO_2NH_2, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $CONH_2$, $CONH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHCO(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), $CO(C_{1-4}$ alkyl), CF_3 or OCF_3;

R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{33} and R^{34} are, independently, hydrogen, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

R^{11}, R^{24} and R^{32} are, independently, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

k and q are, independently, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof; or a solvate thereof.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Halogen includes fluorine, chlorine, bromine and iodine.

Alkyl groups and moieties are straight or branched chain and are, for example, methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

Alkenyl group are, for example, vinyl or allyl.

Cycloalkyl is mono-, bi or tricyclic and is, for example, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.1]heptyl or camphoryl.

Cycloalkenyl is especially monocyclic and is, for example, cyclopentenyl or cyclohexenyl.

Aryl is preferably phenyl or naphthyl.

Heterocyclyl is an aromatic or non-aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Alternatively, heterocyclyl is an aromatic or non-aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur..

Heterocyclyl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, pyridinyl (for example in 6-oxo-1,6-dihydro-pyridinyl), pyrimidinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl (for example

in 1-dioxo-2,3-dihydrobenz[b]thienyl), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl (for example in 1H-benzthiazol-2-one-yl), 2,3-dihydrobenzthiazolyl (for example in 2,3-dihydrobenzthiazol-2-one-yl), 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2a]pyridinyl), thieno[3,2-b]pyridin-6-yl 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, benzofurazan, quinoxalinyl, dihydro-1-benzopyryliumyl (for example in a coumarinyl or a chromonyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example in 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), a purine (for example in 3,7-dihydro-purin-2,6-dione-8-yl), quinolinyl, isoquinolinyl (for example in 2H-isoquinolin-1-one-yl), a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl or in 1H-[1,8]naphthyridin-4-one-yl), a benzothiazinyl (for example in 4H-benzo[1,4]thiazin-3-one-yl), benzo[d]imidazo[2,1-b]thiazol-2-yl or dibenzothiophenyl. Such heterocyclyl groups can, where appropriate, be in the form of an N-oxide (such as pyridine-N-oxide), an S-oxide or an S-dioxide.

Alternatively heterocyclyl is, for example, furyl, thienyl, 2,1,3-benzothiadiazole, 2,1,3-benzoxadiazole, quinoxaline, dihydro-1-benzopyrylium (for example a coumarin, a chromene or a chromone), piperidine, morpholine, pyrrole, indole, indoline, isoindoline, quinoline, thiazole, pyrazole, isoxazole, imidazole, pyridine, benzofuryl, benzimidazole, pyrimidine or dibenzothiophene.

In one aspect T is C=O or CR^7R^8, wherein R^7 and R^8 are, independently, hydrogen or C_{1-4} alkyl (such as methyl).

In another aspect n is 0 or 1.

In a further aspect m is 0.

In a still further aspect X is O.

In another aspect R^1 is phenyl substituted with one or more of fluorine, chlorine, C_{1-4} alkyl (especially methyl) or C_{1-4} alkoxy (especially methoxy).

In a further aspect R^1 is phenyl optionally substituted (for example with one, two or three) by halo (especially fluoro or chloro), C_{1-4} alkyl (especially methyl) or C_{1-4} alkoxy (especially methoxy). In a still further aspect R^1 is phenyl substituted by one, two or three of: fluoro, chloro, methyl or methoxy.

In yet another aspect R^1 is phenyl optionally substituted by halogen (for example fluoro or chloro). The variable R^1 is, for example, 3,4-difluorophenyl or 3,4-dichlorophenyl.

In a still further aspect R^2 and R^3 are both hydrogen.

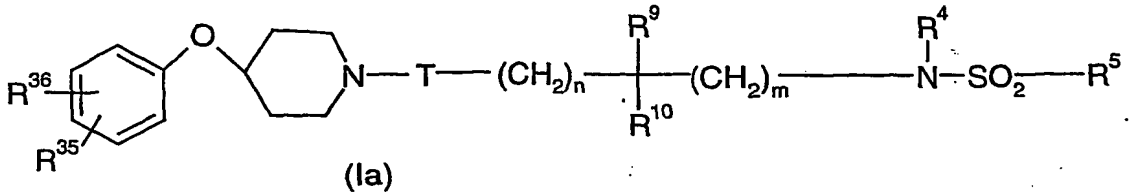
In another aspect R^4 is hydrogen or C_{1-4} alkyl (such as methyl).

In yet another aspect R^9 is hydrogen, C_{1-4} alkyl (such as methyl or iso-propyl) or phenyl(C_{1-4} alkyl) (such as benzyl).

In a still further aspect R^{10} is hydrogen.

In yet another aspect R^5 is C_{1-6} alkyl {optionally substituted by phenyl (itself optionally substituted by halogen or nitro), $CO_2(C_{1-4}$ alkyl), C_{3-10} cycloalkyl (itself optionally substituted by oxo or C_{1-4} alkyl) or heterocyclyl}, aryl (such as phenyl or naphthyl) {optionally substituted by halogen, C_{1-6} alkyl, C_{1-4} alkoxy, OH, nitro, cyano, CF_3, OCF_3, $N(C_{1-4}$ alkyl)$_2$, $NHCO(C_{1-4}$ alkyl), CO_2H or $CO_2(C_{1-4}$ alkyl)} or hererocyclyl (such as thienyl, chromenyl, indolinyl, isoindolinyl, thiazolyl, quinolinyl, pyrazolyl, isoxazolyl or imidazolyl) {optionally substituted by halogen, oxo, C_{1-4} alkyl, $NHCO(C_{1-4}$ alkyl), $CO(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), pyridyl or isoxazolyl}.

In yet another aspect the present invention provides a compound of formula (Ia):



(Ia)

wherein:

T, n, m, R^4, R^5, R^9 and R^{10} are as defined above;

R^{35} is hydrogen, halogen or phenyl (optionally substituted by one or two halogen atoms or by one $CONR^{37}R^{38}$, $NR^{38}COR^{40}$, SO_2R^{41}, $SO_2NR^{42}R^{43}$ or $NR^{44}SO_2R^{45}$ group);

R^{36} is hydrogen or halogen;

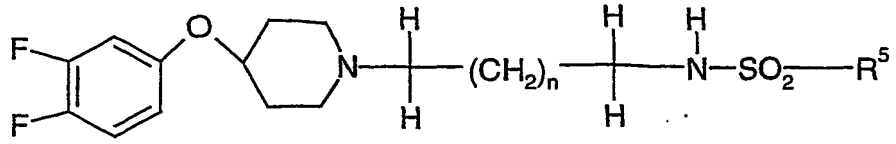
R^{37}, R^{38}, R^{39}, R^{40}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

R^{41} and R^{45} are, independently, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

or a pharmaceutically acceptable salt thereof.

In another aspect R^{35} and R^{36} are both chlorine or both fluorine, especially 3,4 disposed on the phenyl ring to which they are attached.

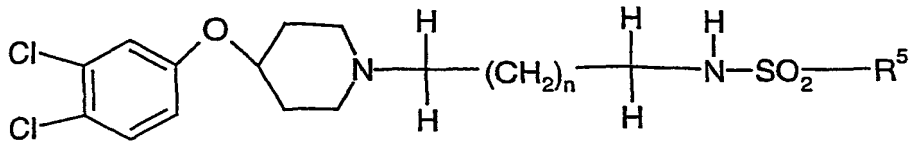
In a further aspect the present invention provides a compound of formula (Ib):



(Ib)

wherein n and R^5 are as defined above.

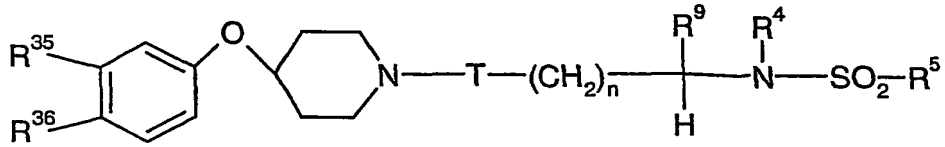
In a still further aspect the present invention provides a compound of formula (Ic):



(Ic)

wherein n and R^5 are as defined above.

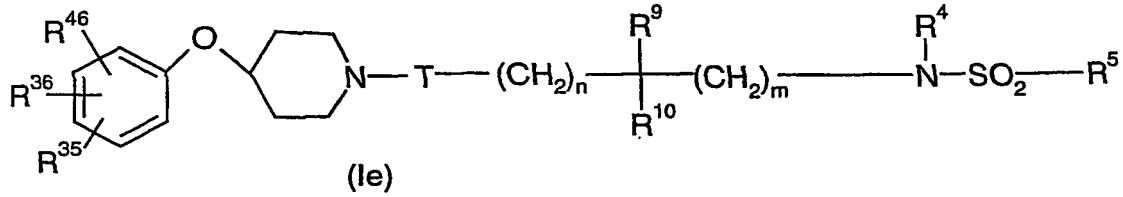
In another aspect the present invention provides a compound of formula (Id):



(Id)

wherein T, n, R^4, R^5, R^9, R^{35} and R^{36} are as defined above. It is preferred that R^{35} and R^{36} are halogen (for example fluoro or chloro).

In a further aspect the present invention provides a compound of formula (Ie):

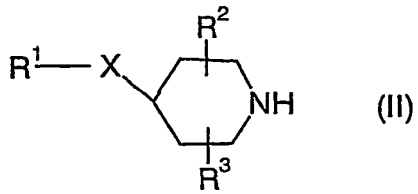


(Ie)

wherein T, n, m, R^4, R^5, R^9 and R^{10} are as defined above; and

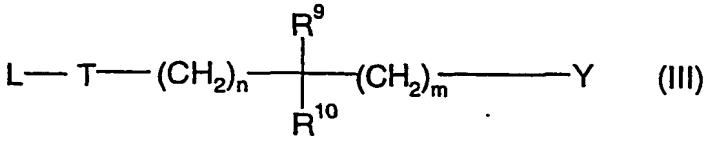
R^{35}, R^{36} and R^{46} are, independently, hydrogen, halogen (especially fluoro or chloro), C_{1-4} alkyl (especially methyl) or C_{1-4} alkoxy (especially methoxy). In a still further aspect R^{35}, R^{36} and R^{46} are, independently, hydrogen, fluoro, chloro, methyl or methoxy, but not all hydrogen.

A compound of formula (I) can be prepared by coupling a compound of formula (II):



(II)

with a compound of formula (III):

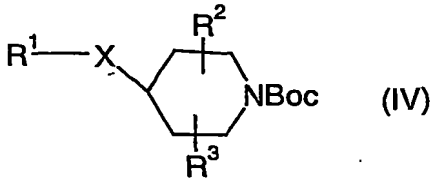


(III)

wherein L is a suitable leaving group, when Y is $NR^4S(O)_2R^5$ then R^4 is not hydrogen, when Y is $S(O)_2NR^4R^5$ then neither R^4 nor R^5 is hydrogen and T is optionally protected during the course of the reaction by a standard protecting group known in the art and deprotected in a separate step or during the reaction work-up. For example:

- when T is carbonyl, L can be OH and the coupling can be carried out in the presence of a coupling agent (such as bromo-tris-pyrrolidino-phosphonium hexafluorophosphate, PYBROP™); or,
- when T is CR^7R^8, L can be chloro or bromo and the coupling can be carrier out in the presence of a suitable base (such as potassium carbonate) in a suitable solvent (such as acetone).

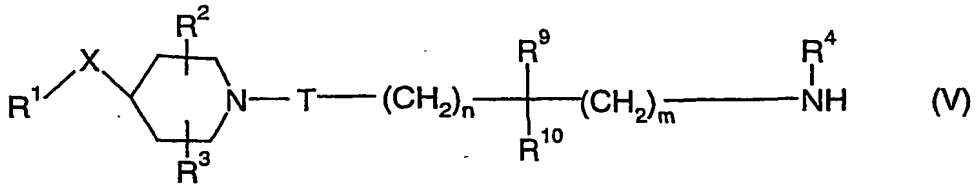
A compound of formula (II) can be prepared by deprotecting a compound of formula (IV):



(IV)

wherein Boc is tert-butoxycarbonyl, for example using trifluoroacetic acid in a suitable solvent (such as dichloromethane) or using a source of hydrogen chloride in a suitable solvent (such as dioxane).

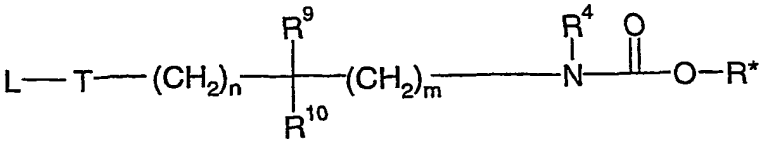
Alternatively, a compound of formula (I), wherein Y is $NR^4S(O)_2R^5$, can be prepared by reacting a compound of formula (V):



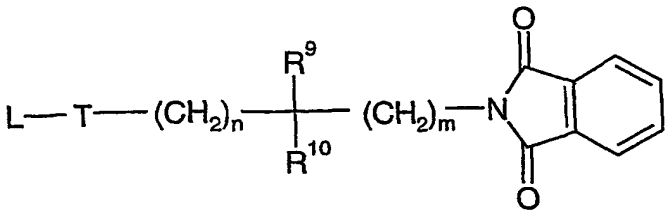
(V)

with a suitable sulphonyl chloride $ClSO_2R^5$.

A compound of formula (V) can be prepared by deprotecting the corresponding carbamate or 1*H*-isoindole-1,3(2*H*)-dione. The corresponding carbamate or 1*H*-isoindole-1,3(2*H*)-dione can be prepared by reacting a compound of formula (II) with a compound of formula (VI) or (VII):



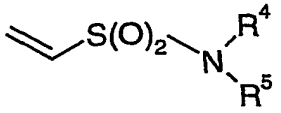
(VI)



(VII)

wherein R* is, for example, C_{1-6} alkyl; and L is as defined above.

A compound of formula (I) wherein m and n are both 0, T is CH_2, R^9 and R^{10} are both hydrogen and Y is $S(O)_2NR^4R^5$, can be prepared by reacting a compound of formula (II) with a compound of formula (IX):



(IX)

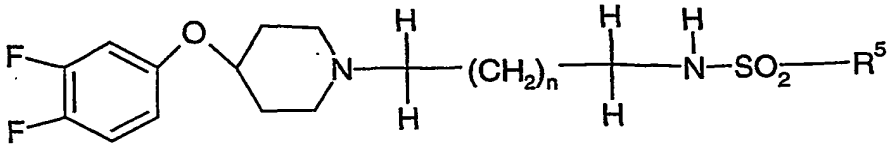
in a suitable solvent (such as an aliphatic alcohol, for example methanol).

Compounds of formula (II), (III), (IV), (VI), (VII) and (IX) can be prepared by using or adapting either methods described in the art or methods described in the Examples.

In another aspect the present invention provides processes, as described herein, for the preparation of compounds of formula (I), (I'), (Ia), (Ib), (Ic), (Id) and (Ie).

The intermediates of formula (V) are provided as a further feature of the invention.

Examples of compounds of formula (Ib) are listed in Table I below.



(Ib)

TABLE I

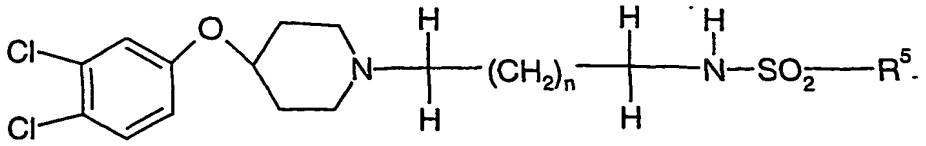
Compound	n	R^5	M+H
1	0	2-OCF_3-C_6H_4	481
2	0	3-NO_2-4-OH-C_6H_3	476
3	0	(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)CH_2	471
4	0	n-Propyl	363

5	0	$C_6(CH_3)_5$	467
6	0	4-n-propyl-C_6H_4	439
7	0	Naphth-2-yl	447
8	0	2,6-Cl_2-C_6H_3	465
9	0	2,6-F_2-C_6H_3	433
10	0	4-NO_2-C_6H_4	442
11	0	2,5-Cl_2-C_6H_3	465
12	0	5-(NMe_2)-naphth-1-yl	490
13	0	2,1,3-benzothiadiazol-4-yl	455
14	0	4-ethyl-C_6H_4	425
15	0	2,5-Cl_2-thien-3-yl	471
16	0	3,4-$(OMe)_2$-C_6H_3	457
17	0	2-Cl-5-CF_3-C_6H_3	499
18	0	5-Cl-thien-2-yl	437
19	0	4-Cl-C_6H_4	431
20	0	4-iso-propyl-C_6H_4	439
21	0	2-Cl-4-CF_3-C_6H_3	499
22	0	2,1,3-benzoxadiazol-4-yl	439
23	0	3-methyl-C_6H_4	411
24	0	iso-propyl	363
25	0	4-CO_2H-C_6H_4	441
26	0	2-oxo-2H-chromen-6-yl	465
27	0	3,4-Cl_2-C_6H_3	465
28	0	2,3-Cl_2-C_6H_3	465
29	0	(2-NO_2-C_6H_4)CH_2	456
30	0	3-CF_3-C_6H_4	465
31	0	4-tert-butyl-C_6H_4	453
32	0	2-NO_2-C_6H_4	442
33		2-F-C_6H_4	415
34	0	3-NO_2-C_6H_4	442
35	0	1-acetyl-indolin-5-yl	480
36	0	Naphth-1-yl	447
37	0	2-OMe-5-Cl-C_6H_3	461

38	0	3-F-C_6H_4	415
39	0	3-Cl-4-($NHCOCH_3$)-C_6H_3	488
40	0	Benzyl	411
41	0	2-NO_2-4-OMe-C_6H_3	472
42	0	2-Me-5-NO_2-C_6H_4	456
43	0	3-CO_2H-C_6H_4	441
44	0	2,4,6-Me_3-C_6H_2	439
45	0	3,4-Cl_2-C_6H_3	465
46	0	4-($NHCOCH_3$)-C_6H_4	454
47	0	2-CF_3-C_6H_4	465
48	0	$(CH_2)_2CO_2CH_3$	407
49	0	4-CH_3-C_6H_4	411
50	0	4-CF_3-C_6H_4	465
51	0	4-CN-C_6H_4	422
52	0	3-NO_2-4-CH_3-C_6H_3	456
53	0	2-($NHCOCH_3$)-4-CH_3-thiazol-5-yl	475
54	0	Quinolin-8-yl	448
55	0	2-OH-3,5-Cl_2-C_6H_2	481
56	0	2,5-$(OMe)_2$-C_6H_3	457
57	0	Phenyl	397
58	0	2-CH_3-4-NO_2-C_6H_3	456
59	0	5-(pyrid-2-yl)-thien-2-yl	480
60	0	1,3-$(CH_3)_2$-5-Cl-pyrazol-4-yl	449
61	0	3,5-$(CH_3)_2$-isoxazol-4-yl	416
62	0	2,3,6-$(CH_3)_3$-4-OMe-C_6H	469
63	0	1-CH_3-imidazol-4-yl	401
64	0	2-OMe-5-Me-C_6H_3	441
65	0	5-(isoxazol-3-yl)-thien-2-yl	470
66	0	2-(CO_2CH_3)-thien-3-yl	461
67	0	4-tert-pentyl-C_6H_4	467
68	0	1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-eth-1-yl	494
69	1	5-(pyridin-2-yl)-thien-2-yl	

TABLE II

Table II comprises 69 compounds of formula (Ic):

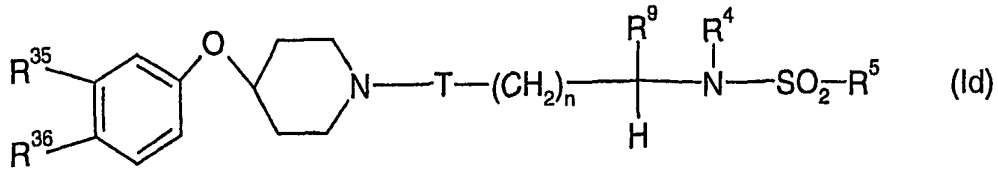


(Ic)

wherein n and R^5 are as defined for the correspondingly numbered compound in Table I.

TABLE III

Table III discloses compounds of formula (Id):



(Id)

wherein the variables are defined in the Table below.

Compound	R^{35}	R^{36}	T	n	R^9	R^4	R^5
1	Cl	Cl	CH_2	1	H	H	2-(pyridin-2-yl)thien-5-yl
2	F	F	C=O	0	(S)-benzyl	H	2-(pyridin-2-yl)thien-5-yl
3	F	F	CH_2	0	(S)-benzyl	H	2-(pyridin-2-yl)thien-5-yl
4	Cl	Cl	CH_2	0	(S)-iso-propyl	H	2-(pyridin-2-yl)thien-5-yl
5	Cl	Cl	CH_2	0	(S)-iso-propyl	H	2,5-$(OCH_3)_2$-C_6H_3
6	F	F	$C(CH_3)_2$	0	H	H	2-(pyridin-2-yl)thien-5-yl
7	F	F	$CHCH_3$	0	H	H	2-(pyridin-2-yl)thien-5-yl
8	F	F	CH_2	0	H	CH_3	2-(pyridin-2-yl)thien-5-yl

The compounds of the invention have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)). Examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia

gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle.

According to a further feature of the invention there is provided a compound of the formula (I), (I'), (Ia), (Ib), (Ic), (Id) or (Ie) or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR3 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof or a solvate thereof.

The invention also provides a compound of the formula (I), (I'), (Ia), (Ib), (Ic), (Id) or (Ie) or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament.

In another aspect the present invention provides the use of a compound of the formula (I), (I'), (Ia), (Ib), (Ic), (Id) or (Ie) or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR3 receptor activity) in a warm blooded animal, such as man).

The invention further provides the use of a compound of formula (I), (I'), (Ia), (Ib), (Ic), (Id) or (Ie) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive

activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a warm blooded animal, such as man.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR3 mediated disease state, especially asthma) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), (I'), (Ia), (Ib), (Ic), (Id) or (Ie) or a pharmaceutically acceptable salt thereof or solvate thereof.

In a further aspect a compound of formula (I), (I'), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including

croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a still further aspect a compound of formula (I), (I'), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma.

The present invention also provides a the use of a compound of formula (I), (I'), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma or rhinitis.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR3 mediated disease state, especially asthma) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), (I'), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof or solvate thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR3 receptor) activity, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), (I'), (Ia), (Ib), (Ic), (Id) or (Ie) or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions,

dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 0.01mgkg^{-1} to 100mgkg^{-1} of the compound, preferably in the range of 0.1mgkg^{-1} to 20mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), (I'), (Ia), (Ib), (Ic), (Id) or (Ie) or a pharmaceutically-acceptable salt thereof (hereafter Compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.0

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β-cyclodextrin may be used to aid formulation.

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300MHz or 400MHz using perdeuterio DMSO (CD_3SOCD_3)or $CDCl_3$ as the solvent unless otherwise stated;

(ii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(iii) the following abbreviations are used:

THF = tetrahydrofuran

DMF = *N*,*N*-dimethylformamide

HPLC = high pressure liquid chromatography

BOC = tert-butoxycarbonyl

TEA = triethylamine

(iv) the title and sub-titled compounds of the examples and methods were named using the ACD/name program from Advanced Chemical Development Inc, Canada;

(v) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry, NovaPak or Ex-Terra reverse phase silica column; and

(vi) solvents were dried with $MgSO_4$ or Na_2SO_4.

Example 1

This Example illustrates the preparation of 4-(3,4-dichlorophenoxy)piperidine.

Step a: tert-Butyl 4-(3,4-dichlorophenoxy)-1-piperidinecarboxylate

Diethyl azodicarboxylate (41.0ml) was added to a solution of triphenylphosphine (62.9g) in tetrahydrofuran (800ml) at 0°C. After 15 minutes 3,4-dichlorophenol (39.1g) was added, after a further 15 minutes tert-butyl 4-hydroxy-1-piperidinecarboxylate (48.3g) in tetrahydrofuran (400ml) was added dropwise over 30 min. The solution was stirred at room temperature for 16 hours and concentrated to a small volume. Purification by flash silica chromatography (ethyl acetate : iso-hexane 95:5) gave the sub-title compound as an oil (61.3g).

MS: APCI(+ve): 246 (M-BOC+2H)

Step b: 4-(3,4-Dichlorophenoxy)piperidine

The product from Example 1, step a) was dissolved in dichloromethane (600ml) and trifluoroacetic acid (300ml) was added. After 24 hours at room temperature the solution was evaporated and the resultant gum triturated under ether to give the sub-titled product as a solid (36.6g). The free base was liberated by addition of aqueous NaOH (2M)

and extraction with ethyl acetate followed by evaporation of solvent to give the title compound as a gum (25g).

^{1}H NMR: δ($CDCl_3$) 1.77 (1H, br s), 2.05-2.26 (4H, m), 3.20-3.49 (4H, m), 4.61 (1H, s), 6.69-7.52 (3H, m).

Example 2

This Example illustrates the preparation of *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propyl}-5-pyridin-2-ylthiophene-2-sulfonamide (Compound 1 of Table III).

Step a: tert-Butyl 3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propylcarbamate

The product from Example 1 Step (b) (10g) was dissolved in DMF (50ml) and triethylamine (14.8ml) was added. tert-Butyl 3-bromopropylcarbamate (10g) was then added and the solution stirred at room temperature for 24 hrs. The solvent was evaporated and the resulting solid dissolved in ethyl acetate and water were added, the organic phase separated, dried, filtered and evaporated to a solid (17.51g).

MS: ESI (+ve): 403 (M+H)

Step b: 3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]propylamine

The product from Example 2 Step (a) (2g) was dissolved in dioxan (100ml) and 6N HCl (100ml) added. After 18hrs at room temperature the solvent was evaporated and the resultant solid basified with NaOH (2M) to pH 11. The aqueous was extracted with ethyl acetate, the organic phase separated, dried, filtered and evaporated to leave the sub-title compound as an oil (1.1g).

MS: ESI (+ve): 303 (M+H)

Step c: *N*-{3-[4-(3,4-dichlorophenoxy)piperidin-1-yl]propyl}-5-pyridin-2-ylthiophene-2-sulfonamide

The product of Example 2, Step (b) (0.2g) was dissolved in acetone (4ml). Potassium carbonate [0.130g dissolved in H_2O (1ml)] was then added, followed by 5-pyridin-2-yl-thiophene-2-sulfonyl chloride (0.171g) and the reaction left to stir for 10 mins. Water was then added and the product extracted with ethyl acetate. The combined organic extracts dried, filtered and concentrated. Purification by reverse phase HPLC {with a gradient eluent system [30% MeCN/NH_4OAc_{aq} (0.1%) to 95% MeCN//NH_4OAc_{aq} (0.1%)]} gave the title compound as a solid (0.135g).

^{1}H NMR: δ ($CDCl_3$) 1.72 (2H, quintet), 1.84-1.91 (2H, m), 1.98-2.04 (2H, m), 2.39-2.47 (2H, m), 2.52 (2H, t), 2.62-2.71 (2H, m), 3.23 (2H, t), 4.32-4.38 (1H, m), 6.75 (1H, dd), 6.99 (1H, d), 7.23 (1H, d), 7.25 (1H, dd), 7.32 (1H, d), 7.49 (1H, d), 7.57 (1H, d), 7.75 (1H, dt), 8.59 (1H, ddd).

Melting point: 115°C

Example 3

This Example illustrates the preparation of *N*-{3-[4-(3,4-difluorophenoxy)-1-piperidinyl]propyl}-5-(2-pyridinyl)-2-thiophenesulfonamide (Compound 69 in Table I).

Step a: tert-Butyl 4-(3,4-difluorophenoxy)-1-piperidinecarboxylate

The sub-title compound was prepared according to the method of Example 1, step (a) using 3,4-difluorophenol to afford an oil (5.4g).

MS: ESI (+ve): 213 (M-BOC+H)

Step b: 4-(3,4-Difluorophenoxy)piperidine

The sub-title compound was prepared according to the method of Example 1, step (b) to afford a pale yellow oil (3g).

MS: ESI (+ve): 214 (M+H)

Step c: 2-{3-[4-(3,4-difluorophenoxy)-1-piperidinyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione

The product from Example 3, Step (b) (1.5g) was dissolved in CH_2Cl_2 (26ml) and triethylamine (1.18ml) was added. 2-(3-Bromopropyl)-1*H*-isoindole-1,3(2*H*)-dione (2.08g) was then added and the solution stirred at room temperature for 12 hrs. Ethyl acetate and aqueous $NaHCO_3$ solution were added and product was extracted with ethyl acetate. The combined organic extracts were dried, filtered and concentrated. This gave the sub-titled product as a solid (1.55g).

MS: APCI(+ve): 401 (M+H)

Step d: 3-[4-(3,4-difluorophenoxy)-1-piperidinyl]propylamine

To the product of Example 3, Step (c) in EtOH (30ml) was added hydrazine monohydrate (0.562ml). The reaction was refluxed for 4 hrs and the solvent evaporated. Dichloromethane (40ml) was added and the solid by-product filtered. The organic residue was evaporated and the product purified by reverse phase HPLC {with a gradient eluent system [25% MeCN/NH_4OAc_{aq} (0.1%) to 95% MeCN//NH_4OAc_{aq} (0.1%)]} to give the sub-title compound as a solid (0.622g).

^{1}H NMR: δ($CDCl_3$) 1.80-1.86 (4H, m) 1.95-2.02 (2H, m), 2.46 (2H, br s), 2.61 (2H, t), 2.75 (2H, br s), 3.04 (2H, t), 4.26 (1H, br s), 6.56-7.27 (5H, m).

Step e: *N*-{3-[4-(3,4-difluorophenoxy)-1-piperidinyl]propyl}-5-(2-pyridinyl)-2-thiophenesulfonamide

The product of Example 3, Step (d) (0.3g) was dissolved in pyridine (1ml) and CH_2Cl_2 (4ml). 5-Pyridin-2-yl-thiophene-2-sulfonyl chloride (0.317g) [dissolved in CH_2Cl_2 (4ml)] was then added and the reaction left to stir for 1 hr. The reaction mixture was poured onto flash silica and the silica flushed with 5%MeOH/94%CH_2Cl_2/1%aq NH_3 as eluent. Evaporation of solvent and purification using reverse phase HPLC {with a gradient eluent system [25% MeCN/NH_4OAc_{aq} (0.1%) to 95% MeCN//NH_4OAc_{aq} (0.1%)]} gave the title compound as a solid (0.120g).

^{1}H NMR: δ(DMSO) 1.50-1.90 (6H, m), 2.07-2.14 (2H, m), 2.27 (2H, t), 2.55-2.61 (2H, m), 2.93 (2H, t), 4.26-4.35 (1H, m), 6.71-8.58 (9H, m)

Melting point: 128-129°C.

Example 4

This Example illustrates the preparation of *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-5-(2-pyridinyl)-2-thiophenesulfonamide (Compound 59 of Table I).

Step a: tert-Butyl 2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethylcarbamate

The product from Example 3, Step (b) (5g) was dissolved in DMF (27ml) and triethylamine (7.7ml) was added. tert-Butyl 2-bromoethylcarbamate (5.8g) was added and the solution stirred at room temperature for 24 hrs. The solvent was evaporated and the residue dissolved in ethyl acetate and washed with water. The organic phase separated, dried, filtered and evaporated. Purification by flash silica chromatography (dichloromethane : methanol 97:3) gave the sub-titled product as an oil (10g) containing a small amount of DMF.

MS: APCI(+ve): 357 (M+H)

Step b: 2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethylamine

The product of Example 4, Step (a) (10g) was dissolved in dioxane (114ml) and HCl (6N) (114ml) was added and the reaction stirred for 2 hrs. The organic solvent was evaporated and aqueous NaOH (2M) added. The product was extracted with ethyl acetate, the combined organic extracts dried, filtered and concentrated to give the sub-title product as an oil (4.65g).

^{1}H NMR: δ($CDCl_3$) 1.74-1.83 (2H, m), 1.95-2.00 (2H, m), 2.26-2.31 (2H, m), 2.43 (2H, t), 2.73 (2H, br s), 2.79 (2H, t), 4.17-4.23 (1H, m), 6.58-7.07 (3H, m).

MS: APCI(+ve): 257 (M+H)

Step c: *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-5-(2-pyridinyl)-2-thiophenesulfonamide

To a solution of 5-pyridin-2-yl-thiophene-2-sulfonyl chloride (0.213g) [in CH_2Cl_2 (10ml)] was added a solution of the product of Example 4, Step (b) (0.210g) [in CH_2Cl_2 (5ml) and pyridine (0.066ml)]. The reaction was left to stir for 12 hrs. The reaction mixture was washed with saturated aqueous NaCl solution and the organics separated and dried and then filtered. The solvents were evaporated and the product purified by using reverse phase HPLC {with a gradient eluent system [25% MeCN/NH_4OAc_{aq} (0.1%) to 95% MeCN//NH_4OAc_{aq} (0.1%)]} give the title compound as a solid (0.03g).

^{1}H NMR: δ ($CDCl_3$) 1.69-1.79 (2H, m), 1.86-1.92 (2H, m), 2.22-2.26 (2H, m), 2.51 (2H, t), 2.53-2.60 (2H, m), 3.15 (2H, t), 4.15-4.24 (1H, m), 6.55-6.57 (1H, m), 6.66-6.70 (1H, m), 7.03 (1H, q), 7.24-7.27 (1H, m), 7.49-7.51 (1H, m), 7.60-7.61 (1H, m), 7.68 (1H, d), 7.75 (1H, t), 8.59 (1H, d).

Melting point: 144-145°C.

Example 5

This Example illustrates the preparation of *N*-{(1*S*)-1-benzyl-2-[4-(3,4-difluorophenoxy)-1-piperidinyl]-2-oxoethyl}-5-(2-pyridinyl)-2-thiophenesulfonamide (Compound 2 of Table III).

Step a: tert-Butyl (1*S*)-1-benzyl-2-[4-(3,4-difluorophenoxy)-1-piperidinyl]-2-oxoethylcarbamate

The product of Example 3, Step (b) (1g) was dissolved in CH_2Cl_2 (20ml) and (2*S*)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoic acid (1.24g), *N*,*N*-di-iso-propylethylamine (2.45ml) and PyBrop (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate, 3.2g) were added. After 1 hr at room temperature CH_2Cl_2 was added and the mixture washed with HCl (2N), aqueous $NaHCO_3$ solution, and saturated aqueous NaCl solution. The organic phase was dried, filtered and evaporated. Purification by flash silica chromatography (hexane : ethyl acetate 70:30) gave the sub-titled product as solid (1.6g).

MS: ESI(+ve): 461 (M+H)

Step b: (1*S*)-1-Benzyl-2-[4-(3,4-difluorophenoxy)-1-piperidinyl]-2-oxoethylamine

The product from Example 5, Step (a) (1.2g) was dissolved in dichloromethane (10ml) and trifluoroacetic acid (5ml) was added. After 1 hr at room temperature the solution was evaporated and aqueous NaOH (2M) added. The product was extracted with ethyl acetate, the combined organic extracts dried, filtered and concentrated to give the sub-title product as an oil (1g).

MS: ESI(+ve): 361 (M+H)

Step c: *N*-{(1*S*)-1-benzyl-2-[4-(3,4-difluorophenoxy)-1-piperidinyl]-2-oxoethyl}-5-(2-pyridinyl)-2-thiophenesulfonamide

To a solution of 5-pyridin-2-yl-thiophene-2-sulfonyl chloride (0.072g) [in CH_2Cl_2 (5ml) and dimethyl amino pyridine (0.034g)] was added a solution of the product of Example 5, Step (b) (0.100g) in CH_2Cl_2 (1ml). The reaction was left to stir for 12 hrs. The reaction mixture was then pre-absorbed onto flash silica and purified by flash silica column chromatography with 2%MeOH/97.5%CH_2Cl_2/0.5%aq NH_3 as eluent. Further purification using flash silica chromatography with 10%MeCN/2%TEA/88%CH_2Cl_2 eluent gave the title compound as a solid (0.045g).

^{1}H NMR: δ ($CDCl_3$) 1.23-1.73 (4H, m), 2.97 (2H, d), 2.93-3.55 (4H, m), 4.05-4.15 (1H, m), 4.55-4.60 (1H, m), 5.94 (1H, s), 6.31-8.57 (14H, m).

MS: APCI(+ve): 584 (M+H).

Example 6

This Example illustrates the preparation of *N*-{(1*S*)-1-benzyl-2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-5-(2-pyridinyl)-2-thiophenesulfonamide (Compound 3 of Table III).

Step a: (1*S*)-1-Benzyl-2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethylamine

The product from Example 5, Step (b) (0.1g) was dissolved in THF (3ml) and borane [0.84 ml (1M in THF)] was added. The reaction was stirred for 1 hr and then quenched slowly with methanol. The solvents were evaporated and the residue re-dissolved in 50%H_2O/50%conc HCl (2ml) and refluxed for 1 hr. The solvents were evaporated. The free base was liberated by addition of aqueous NaOH (2M) and extraction with ethyl acetate followed by drying, filtration and evaporation of solvent to give the sub-title compound as an oil (0.092g).

MS: APCI(+ve): 347 (M+H)

Step b: *N*-{(1*S*)-1-benzyl-2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-5-(2-pyridinyl)-2-thiophenesulfonamide

The product of Example 6, Step (a) (0.091g) was dissolved in acetone (2ml). Potassium carbonate [0.066g dissolved in H_2O (0.5ml)] was then added, followed by 5-pyridin-2-yl-thiophene-2-sulfonyl chloride (0.067g) and the reaction left to stir for 10 mins. Water was then added and the product extracted with ethyl acetate. The combined organic extracts dried, filtered and concentrated. Purification by flash silica column chromatography with 1%MeOH/98.9%CH_2Cl_2/0.1%aq NH_3 as eluent, and then reverse phase HPLC {with a gradient eluent system [50% MeCN/NH_4OAc_{aq} (0.1%) to 70% MeCN//NH_4OAc_{aq} (0.1%)]} gave the title compound as a solid (0.057g).

^{1}H NMR: δ ($CDCl_3$) 1.61 (2H, m), 1.71-1.81 (2H, m), 2.00-2.09 (2H, m), 2.20-2.26 (2H, m), 2.30-2.38 (2H, m), 2.82-2.88 (1H, dd), 3.24-3.29 (1H, dd), 3.45-3.51 (1H, m), 4.08 (1H, m), 6.47-6.50 (1H, m), 6.62 (1H, m), 6.95 (1H, q), 7.19-7.30 (6H, m), 7.50-7.51 (1H, m), 7.61-7.62 (1H, m), 7.66 (1H, d), 7.74 (1H, t), 8.58 (1H, m).

MS: APCI(+ve): 570 (M+H)

Example 7

This Example illustrates the preparation of *N*-((1*S*)-1-{[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl}-2-methylpropyl)-5-(2-pyridinyl)-2-thiophenesulfonamide (Compound 4 of Table III).

Step a: tert-Butyl (1*S*)-1-{[4-(3,4-dichlorophenoxy)-1-piperidinyl]carbonyl}-2-methylpropylcarbamate

To (2*S*)-2-[(tert-butoxycarbonyl)amino]-3-methylbutanoic acid (1.13g) in CH_2Cl_2 (5 ml) was added 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (0.99g) and left to stir for 5 mins. The product of Example 1, Step (b) (0.98g) dissolved in CH_2Cl_2 (5ml) was then and the reaction left to stir for 3 hrs. Aqueous $NaHCO_3$ solution was added and the product extracted with ethyl acetate. The organic phase was dried, filtered and evaporated to give the sub-title compound (1.57g).

MS: APCI(+ve): 345(M-BOC+H)

Step b: (1*S*)-1-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]carbonyl}-2-methylpropylamine

The product from Example 7, Step (a) (1.57g) was dissolved in dichloromethane (14ml) and trifluoroacetic acid (4ml) was added. After 2 hours at room temperature the solution was evaporated and aqueous NaOH (2M) was added. The product was extracted

with ethyl acetate, the combined organic extracts dried, filtered and concentrated to give the sub-title product as an oil (1.12g).

MS: APCI(+ve): 345 (M+H)

Step c: (1*S*)-1-{[4-(3,4-Dichlorophenoxy)-1-piperidinyl]methyl}-2-methylpropylamine

The product from Example 7, Step (b) (1.12g) was dissolved in THF (10ml) and borane [22.7ml (1M in THF)] was added. The reaction was stirred for 2 hr and the solvents evaporated. The reaction was quenched slowly with MeOH followed by aqueous HCl (5ml Concentrated HCl: 5ml H_2O). The MeOH was evaporated and NaOH (2M) added until pH 9 was reached. The product was extracted with ethyl acetate and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried, filtered and solvents evaporated to give the sub-title compound as an oil (0.98g).

MS: APCI(+ve): 331 (M+H)

Step d: *N*-((1*S*)-1-{[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl}-2-methylpropyl)-5-(2-pyridinyl)-2-thiophenesulfonamide.

The product of Example 7, Step (c) (0.050g) was dissolved in acetone (1ml). K_2CO_3 [0.033g dissolved in H_2O (0.5ml)] was then added, followed by 5-pyridin-2-yl-thiophene-2-sulfonyl chloride (0.041g) and the reaction left to stir for 1 hr. Water was then added and the product extracted with ethyl acetate. The combined organic extracts dried, filtered and concentrated. Purification by flash silica column chromatography with 30%EtOAc/68%Hexane/2%TEA as eluent, and then reverse phase HPLC [(50% $MeCN/NH_4OAc_{aq}$ (0.1%)] gave the title compound as a solid (0.023g).

^1H NMR: δ ($CDCl_3$) 0.88-0.94 (7H, m), 1.60-1.71 (2H, m), 1.76-1.87 (2H, m), 2.17-2.27 (2H, m), 2.32-2.38 (2H, m), 2.43-2.47 (2H, m), 3.22-3.28 (1H, m), 4.15-4.22 (1H,m), 6.68 (1H, dt), 6.90-6.92 (1H, m), 7.23-7.29 (2H, m), 7.50 (1H, t), 7.59 (1H, t), 7.65-7.67 (1H, m), 7.71-7.75 (1H, m), 8.58 (1H, m).

MS: APCI(+ve): 554 (M+H)

Example 8

This Example illustrates the preparation of *N*-((1*S*)-1-{[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl}-2-methylpropyl)-2,5-dimethoxybenzenesulfonamide (Compound 5 of Table III).

The product of Example 7, Step (b) (0.050g) was dissolved in acetone (1ml), K_2CO_3 [0.033g dissolved in H_2O (0.3ml)] was then added, followed by 2,5-dimethoxy-

benzenesulfonyl chloride (0.039g). The reaction left stirring for 30 mins. Water was then added and the product extracted with ethyl acetate. The combined organic extracts were dried, filtered and concentrated. Purification by flash silica column chromatography with 1%MeOH/98.9%CH_2Cl_2/0.1%aq NH_3 as eluent gave the title compound as a solid (0.072g).

^{1}H NMR: δ ($CDCl_3$) 0.85-0.90 (6H, m), 1.48-1.72 (5H, m), 2.25 (4H, m), 2.48 (2H, m), 3.20 (1H, m), 3.81 (3H, s), 3.95 (3H, s), 4.14 (1H, m), 5.28 (1H, m), 6.70-6.95 (1H, m), 6.95-6.98 (2H, m), 7.04-7.07 (1H, m), 7.26-7.31 (1H, m), 7.44 (1H, m).

MS: APCI(+ve): 531 (M+H)

Example 9

This Example illustrates the preparation of *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]-2-methylpropyl}-5-(2-pyridinyl)-2-thiophenesulfonamide (Compound 6 of Table III).

Step a: 2-[4-(3,4-dichlorophenoxy)-1-piperidinyl]-2-methyl-1-propanamine

The product of Example 3, Step (b) (1.5g) was dissolved in acetone (1ml). After five minutes 2-hydroxy-2-methylpropanenitrile (0.64ml) was added and the reaction left to stir for 12 hrs. The solvent was allowed to evaporate and then THF (10ml) was added followed by $LiAlH_4$ (1M in THF, 20ml) and the reaction left to stir overnight. The reaction was then quenched with H_2O (0.5ml), followed by NaOH (15% solution in H_2O, 0.5ml) and then H_2O (1.5ml). Ethyl acetate was then added and the mixture dried and filtered. The organics were evaporated and purification by flash silica column chromatography with 10%MeOH/90%CH_2Cl_2 as eluent gave the sub-title compound as an oil (0.60g).

^{1}H NMR: δ ($CDCl_3$) 1.01 (6H, s), 1.45 (2H, br s), 1.69-1.79 (2H, m), 1.96-2.00 (2H, m), 2.30-2.40 (2H, m), 2.58 (2H, m), 2.79-2.81 (2H, m), 4.14-4.19 (1H, m), 6.56-7.09 (3H, m).

MS: ESI(+ve): 285 (M+H)

Step b: *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]-2-methylpropyl}-5-(2-pyridinyl)-2-thiophenesulfonamide

Prepared by the method of Example 7, Step (d) using the product of Example 9, Step (a) to give the title compound as a solid (0.137g).

^{1}H NMR: δ (DMSO) 0.98 (6H, s), 1.51-1.59 (2H,m), 1.85-1.89 (2H, m), 2.24-2.33 (2H, m), 2.67-2.70 (2H, m), 2.86 (2H, s), 4.24-4.31 (1H, m), 6.71-8.58 (10H, m).

Melting point: 133-134°C.

Example 10

This Example illustrates the preparation of *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]propyl}-5-(2-pyridinyl)-2-thiophenesulfonamide (Compound 7 of Table III).

Step a: *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]propyl}-2-phenylacetamide

The product of Example 3, Step (b) (0.8g) was dissolved in 1,2-dichloroethane (14ml). *N*-(2-oxopropyl)-2-phenylacetamide was added (0.72g) followed by $NaBH(OAc)_3$ (1.12g) and acetic acid (0.12g). After 18 hours at room temperature aqueous NaOH (1M) solution and ethyl acetate were added. The product was extracted ethyl acetate, the combined organic extracts dried, filtered and concentrated. Purification by flash silica column chromatography (dichloromethane : methanol 95:5) gave the sub-title compound (0.77g).

MS: APCI(+ve): 389 (M+H)

Step b: 2-[4-(3,4-Difluorophenoxy)-1-piperidinyl]-1-propanamine

To the product of Example 10, Step (a) (0.772g) was added 50%conc HCl/50%MeOH (20ml) and the reaction heated to 60°C for 2 days. Evaporation of solvent and purification by flash silica column chromatography using 10%MeOH/88.9%CH_2Cl_2/0.1%aq. NH_3 as eluent gave the sub-title compound (0.282g).

Step c: *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]propyl}-5-(2-pyridinyl)-2-thiophenesulfonamide.

Prepared by the method of Example 7, Step (d) using the product of Example 10, Step (b) to give the title compound as a solid (0.21g).

^{1}H NMR: δ (DMSO) 0.91 (3H, d), 1.48-1.59 (2H, m), 1.84-1.89 (2H, m), 2.22-2.39 (2H, m), 2.56-2.61 (2H, m), 2.78-2.84 (1H, m), 2.91-2.98 (1H, m), 3.32 (1H, br s), 4.24-4.32 (1H, m), 6.71-8.59 (9H, m).

Melting point: 153-154°C.

Example 11

This Example illustrates the preparation of *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-*N*-methyl-5-(2-pyridinyl)-2-thiophenesulfonamide (Compound 8 of Table III).

Step a: *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-2,2,2-trifluoroacetamide

To the product of Example 4, Step (b) dissolved in CH_2Cl_2 (20ml) with triethylamine (2.45ml) at 0°C was added trifluoroacetic anhydride (1.24ml) in CH_2Cl_2 (5ml). The reaction was allowed to warm to room temperature over 1 hr. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. The combined organics were dried, filtered and solvents evaporated. Purification by flash silica column chromatography using 2%MeOH/97.6%CH_2Cl_2/0.4%aq. NH_3 as eluent gave the sub-title product (1.64g).

MS: ESI(+ve): 353 (M+H)

Step b: *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-2,2,2-trifluoro-*N*-methylacetamide

The product of Example 11, Step (a) (1.64g) dissolved in THF (5 ml) was added dropwise to a suspension of NaH (60% dispersion in oil, 0.205g) in THF (20 ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 30 mins then cooled to 0°C and methyl iodide (0.290ml) dissolved in THF (5ml) added dropwise. The reaction was then allowed to warm to room temperature and left for 12 hrs. Two further aliquots of methyl iodide (0.2ml and 0.5ml) were added over 12 hrs. The reaction was quenched with saturated $NaHCO_3$ and the product extracted with ethyl acetate, dried, and filtered. Evaporation of solvent and purification by flash silica column chromatography using 1%MeOH/98.5%CH_2Cl_2/0.5%aq. NH_3 as eluent gave the sub-title product (0.30g).

MS: ESI(+ve): 367 (M+H)

Step c: *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-*N*-methylamine

The product of Example 11, Step (b) (0.3g) was dissolved in EtOH (15 ml) and NaOH (2M, 5 ml) added. The reaction was stirred for 48 hrs and H_2O and EtOAc added. The organic layer was washed with saturated aqueous NaCl solution, dried, filtered and evaporated to give an oil (0.221g).

MS: ESI(+ve): 271 (M+H)

Step d: *N*-{2-[4-(3,4-difluorophenoxy)-1-piperidinyl]ethyl}-*N*-methyl-5-(2-pyridinyl)-2-thiophenesulfonamide hydrochloride.

Prepared by the method of Example 7, Step (d) using the product of Example 11, Step (c) with Et_2O/HCl to give the title compound as a hydrochloride salt (0.073g).

^{1}H NMR: δ (D_2O) 1.96-2.43 (2H, m), 2.92 (3H, s), 3.26-3.28 (1H, m), 3.41-3.63 (7H, m), 3.81-3.84 (1H, m), 6.82-6.87 (1H, m), 6.99-7.05 (1H, m), 7.23 (1H, m), 7.69 (1H, td), 7.83 (1H, d), 7.86 (1H, d), 8.08 (1H, d), 8.22 (1H, td), 8.60 (1H, ddd).
Melting point: 123°C.

Example 12

This Example illustrates the preparation of 2-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-*N*-[4-(methylsulfonyl)phenyl]ethanesulfonamide.

Step a: *N*-[4-(methylsulfonyl)phenyl]ethylenesulfonamide

To a suspension of 4-(methylsulfonyl)aniline (0.378g) in diethyl ether (10 ml) and triethylamine (0.462ml) at 0°C was added 2-chloroethanesulfonyl chloride (0.346ml). The reaction mixture was left to stir at 0°C for 3hrs and then at room temperature for 8hrs. The solvent was evaporated to give the sub-title compound as a brown solid which was used without further purification in Example 12, step b.
MS: ES(-ve): 260 (M-H)

Step b: 2-[4-(3,4-dichlorophenoxy)piperidin-1-yl]-*N*-[4-(methylsulfonyl)phenyl] ethanesulfonamide.

The product from Example 12, step a was dissolved MeOH (10ml) and the product of Example 1, step b) added, and the reaction stirred at room temperature for 2hrs. The reaction mixture was then poured into water and the product extracted with dichloromethane. The combined organic extracts were washed with water and brine, then dried, filtered and concentrated. Purification by reverse phase HPLC {with a gradient eluent system [40% MeCN/NH_4OAc_{aq} (0.1%) to 95% MeCN//NH_4OAc_{aq} (0.1%)]}. Any excess NH_4OAc in the product was removed by dissolving the compound in ethyl acetate and washing with aqueous saturated $NaHCO_3$ followed by drying of the organics, filtration and evaporation of solvent. This gave the title compound (0.052g).

^{1}H NMR: δ(DMSO) 1.38 - 1.49 (2H, m), 1.72 - 1.82 (2H, m), 2.14 - 2.22 (2H, m), 2.52 - 2.62 (2H, m), 2.66 - 2.76 (2H, m), 3.20 (3H, s), 3.38 - 3.47 (2H, m), 4.30 - 4.42 (1H, m), 6.89 - 6.98 (1H, m), 7.22 (1H, d), 7.38 (2H, d), 7.48 (1H, d), 7.85 (2H, d).
MS: APCI(+ve): 507 (M+H)

Example 13

Pharmacological Analysis: Calcium flux $[Ca^{2+}]_i$ assay

Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended ($5x10^6$ ml^{-1}) and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/ml (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, $MgSO_4$ 0.8mM, glucose 5.5mM, Na_2CO_3 8.5mM, KCl 5mM, HEPES 20mM, $CaCl_2$ 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5x10^6$ ml^{-1}. The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with 5μM fibronectin for two hours) at 25μl/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of eotaxin and the transient increase in fluo-3 fluorescence (l_{Ex} =490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

Human eosinophil chemotaxis

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at $10x10^6$ ml^{-1} in RPMI containing 200 IU/ml penicillin, 200 μg/ml streptomycin sulphate and supplemented with 10% HIFCS, at room temperature.

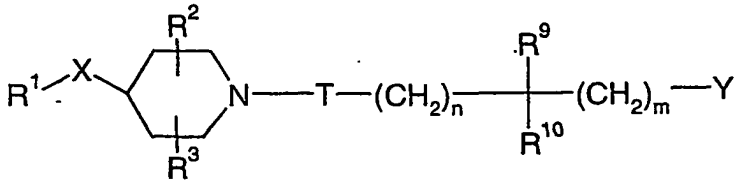
Eosinophils (700 μl) were pre-incubated for 15 mins at 37° C with 7 μl of either vehicle or compound (100x required final concentration in 10% DMSO). The chemotaxis plate (ChemoTx, 3μm pore, Neuroprobe) was loaded by adding 28μl of a concentration of eotaxin (0.1 to 100nM) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 μl of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO_2 atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 µl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Certain compounds of the Examples were found to be antagonists of the eotaxin mediated human eosinophil chemotaxis.

CLAIMS

1. A compound of formula (I):



(I)

wherein: m and n are, independently, 0, 1, 2, 3 or 4; X is CH_2, CO, O, S, S(O), $S(O)_2$ or NR^6; Y is $NR^4S(O)_2R^5$ or $S(O)_2NR^4R^5$; T is C=O or CR^7R^8; R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl; R^2 and R^3 are, independently, hydrogen or C_{1-6} alkyl; R^4 and R^6 are, independently, hydrogen or C_{1-6} alkyl (optionally substituted with aryl); R^5 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^{11}, aryl or heterocyclyl}, C_{3-10} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, C_{3-7} cycloalkenyl {optionally substituted by C_{1-6} alkyl or aryl}, aryl or heterocyclyl; or, when Y is $S(O)_2NR^4R^5$, R^5 may also be hydrogen; R^7, R^8, R^9 and R^{10} are, independently, hydrogen or C_{1-6} alkyl (optionally substituted with aryl); wherein the foregoing aryl and heterocyclyl moieties are, independently, optionally substituted by one or more of halo, cyano, nitro, hydroxy, $S(O)_qR^{11}$, $OCONR^{12}R^{13}$, $NR^{14}R^{15}$, $NR^{16}COR^{17}$, $NR^{18}CONR^{19}R^{20}$, $SO_2NR^{21}R^{22}$, $NR^{23}SO_2R^{24}$, $CONR^{25}R^{26}$, COR^{27}, CO_2R^{28}, $OCOR^{29}$, $NR^{30}CO_2R^{31}$, C_{1-6} alkyl (itself optionally substituted with halo, C_{1-6} alkoxy, C_{3-10} cycloalkyl, $CO_2(C_{1-6}$ alkyl), $OCO(C_{1-6}$ alkyl), SO_2R^{32}, $CONR^{33}R^{34}$, phenyl, phenoxy, heterocyclyl or heterocyclyloxy), C_{3-10} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, methylenedioxy, phenyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, heterocyclyl, heterocyclyloxy or heterocyclyl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heterocyclyl moieties are optionally substituted with halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, SO_2NH_2, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $CONH_2$, $CONH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHCO(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), $CO(C_{1-4}$ alkyl), CF_3 or OCF_3; R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{33} and R^{34} are, independently, hydrogen, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy); R^{11}, R^{24} and R^{32} are, independently, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or

C_{1-6} haloalkoxy); k and q are, independently, 0, 1 or 2; or a pharmaceutically acceptable salt thereof; or a solvate thereof.

2. A compound of formula (I) as claimed in claim 1 wherein aryl is phenyl.

3. A compound of formula (I) as claimed in claim 1 or 2 wherein heterocyclyl is furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, pyridinyl, pyrimidinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl, indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl, 1,2,3-benzothiadiazolyl, an imidazopyridinyl, thieno[3,2-b]pyridin-6-yl 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, benzofurazan, quinoxalinyl, dihydro-1-benzopyryliumyl, 3,4-dihydro-1H-2,1-benzothiazinyl, a pyrazolopyridine, a purine, quinolinyl, isoquinolinyl, a naphthyridinyl, a benzothiazinyl, benzo[d]imidazo[2,1-b]thiazol-2-yl or dibenzothiophenyl; or such a group, where appropriate, in the form of an N-oxide, an S-oxide or an S-dioxide.

4. A compound of formula (I) as claimed in claim 1, 2 or 3 wherein T is C=O or CR^7R^8, wherein R^7 and R^8 are, independently, hydrogen or C_{1-4} alkyl.

5. A compound of formula (I) as claimed in claim 1, 2, 3 or 4 wherein n is 0 or 1.

6. A compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 wherein m is 0.

7. A compound of formula (I) as claimed in any one of the preceding claims wherein X is O.

8. A compound of formula (I) as claimed in any one of the preceding claims wherein R^1 is phenyl substituted with one or more of fluorine, chlorine, C_{1-4} alkyl or C_{1-4} alkoxy.

9. A compound of formula (I) as claimed in any one of the preceding claims wherein R^2 and R^3 are both hydrogen.

10. A compound of formula (I) as claimed in any one of the preceding claims wherein R^4 is hydrogen or C_{1-4} alkyl.

11. A compound of formula (I) as claimed in any one of the preceding claims whereinR^9 is hydrogen, C_{1-4} alkyl or phenyl(C_{1-4} alkyl).

12. A compound of formula (I) as claimed in any one of the preceding claims wherein R^{10} is hydrogen.

13. A compound of formula (I) as claimed in any one of the preceding claims wherein R^5 is C_{1-6} alkyl {optionally substituted by phenyl (itself optionally substituted by halogen or nitro), $CO_2(C_{1-4}$ alkyl), C_{3-10} cycloalkyl (itself optionally substituted by oxo or C_{1-4} alkyl) or heterocyclyl}, aryl {optionally substituted by halogen, C_{1-6} alkyl, C_{1-4} alkoxy, OH, nitro, cyano, CF_3, OCF_3, $N(C_{1-4}$ alkyl$)_2$, $NHCO(C_{1-4}$ alkyl), CO_2H or $CO_2(C_{1-4}$ alkyl)} or hererocyclyl {optionally substituted by halogen, oxo, C_{1-4} alkyl, $NHCO(C_{1-4}$ alkyl), $CO(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), pyridyl or isoxazolyl}.

14. A compound of formula (I) as claimed in any one of the preceding claims wherein Y is $NR^4S(O)_2R^5$.

15. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof, as claimed in claim 1, and a pharmaceutically acceptable adjuvant, diluent or carrier.

16. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof, as claimed in claim 1, for use as a medicament.

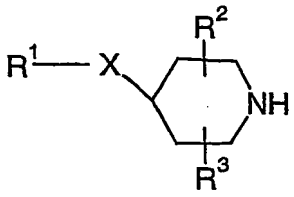
17. The use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof, as claimed in claim 1, in the manufacture of a medicament for use in therapy.

18. A method of treating a CCR3 mediated disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically

effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1.

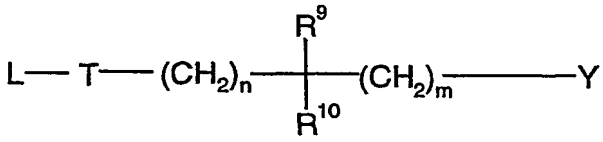
19. A process for preparing a compound of formula (I) as claimed in claim 1, the process comprising:

a) coupling a compound of formula (II):



(II)

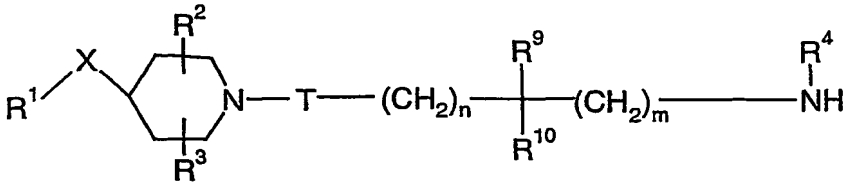
with a compound of formula (III):



(III)

wherein L is a suitable leaving group, when Y is $NR^4S(O)_2R^5$ then R^4 is not hydrogen, when Y is $S(O)_2NR^4R^5$ then neither R^4 nor R^5 is hydrogen and T is optionally protected during the course of the reaction by a standard protecting group;

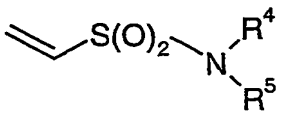
b) for preparing a compound of formula (I) wherein Y is $NR^4S(O)_2R^5$, reacting a compound of formula (V):



(V)

with a suitable sulphonyl chloride of formula $ClSO_2R^5$; or,

c) for preparing a compound of formula (I) wherein m and n are both 0, T is CH_2, R^9 and R^{10} are both hydrogen and Y is $S(O)_2NR^4R^5$, reacting a compound of formula (II) with a compound of formula (IX):



(IX)

in a suitable solvent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01298

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 211/46, C07D 405/12, C07D 409/12, C07D 417/12, C07D 401/12, A61K 31/4468

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9904794 A1 (MERCK & CO. INC.), 4 February 1999 (04.02.99) --	1-17,19
X	Journal of Medicinal Chemistry, Vol 41, No 5, 1998. Ian T. Forbes: "(R)-3,N-Dimethyl-N-[1-methyl-3-(4-methyl-piperidin-1-yl)propyl]benzenesulfonamide: The First Selective 5-HT 7 Receptor Antagonist" pages 655-657 --	1-6,8-17,19
X	J. Med. Chem., Vol 36, 1993, Jean-Luc Malleron et al: "New Indole Derivatives as Potent and Selective Serotonin Uptake Inhibitors", pages 1194-1202 --	1,3-6,10-17, 19

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 November 2001	07 -11- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01298

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Bioorganic & Medicinal Chemistry Letters, Vol 10, 15 May 2000, Maria L. López-Rodriguez et al: First Pharmacophoric Hypothesis for 5-HT 7 Antagonism" pages 1097-1100	1-6,8-17,19
	--	
X	WO 9614317 A1 (J. URIACH & CIA S.A.), 17 May 1996 (17.05.96)	1-6,9-17,19
	--	
X	EP 0429341 A2 (RHONE-POULENC SANTE), 29 May 1991 (29.05.91)	1,3-6,10-17, 19
	--	
X	FR 2675801 A1 (RHONE-POULENC RORER S.A.), 30 October 1992 (30.10.92)	1,3-6,10-17, 19
	--	

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE 01/01298

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9904794 A1	04/02/99	AU 8576098 A	16/02/99
		EP 0971887 A	19/01/00
		EP 1003514 A	31/05/00
		GB 9800958 D	00/00/00
		US 6258851 B	10/07/01
		US 6136827 A	24/10/00
WO 9614317 A1	17/05/96	AT 192152 T	15/05/00
		AU 3563695 A	31/05/96
		CA 2180660 A	17/05/96
		DE 69516503 D,T	15/03/01
		DK 738269 T	28/08/00
		EP 0738269 A,B	23/10/96
		SE 0738269 T3	
		ES 1028940 U,Y	01/04/95
		ES 2087038 A,B	01/07/96
		ES 2147616 T	16/09/00
		GR 3033528 T	29/09/00
		JP 9507862 T	12/08/97
		NO 306345 B	25/10/99
		NO 962855 A	05/07/96
		PT 738269 T	31/08/00
		US 5705504 A	06/01/98
EP 0429341 A2	29/05/91	AU 624280 B	04/06/92
		AU 6675490 A	20/06/91
		CA 2030238 A	21/05/91
		FI 905700 A	21/05/91
		FR 2654729 A,B	24/05/91
		HU 59389 A	28/05/92
		HU 907200 D	00/00/00
		IE 904165 A	22/05/91
		IL 96405 D	00/00/00
		JP 3190858 A	20/08/91
		NO 905008 A	21/05/91
		PL 287845 A	24/02/92
		PT 95938 A	30/09/91
		US 5114949 A	19/05/92
		ZA 9009297 A	29/01/92
		FR 2656306 A	28/06/91
		FR 2663635 A	27/12/91
FR 2675801 A1	30/10/92	NONE	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01298

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18
because they relate to subject matter not required to be searched by this Authority, namely:

En metod för behandling av människo- eller djurkroppar genom terapi, se regel 39.1

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.